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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/904,532	07/13/2001	Avi Ashkenazi	10466/50	2313

35489 7590 08/27/2003

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EXAMINER
DEBERRY, REGINA M

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 08/27/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/904,532	ASHKENAZI ET AL.	
	Examiner	Art Unit	
	Regina M. DeBerry	1647	

-- The MAILING DATE of this communication appears on the c ver sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 May 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *39-47 and 49-51* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *39-47,50 and 51* is/are rejected.

7)☒ Claim(s) *49* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Status of Application, Amendments and/or Claims

The amendment filed 11 February 2003 (Paper No. 16) has been entered in full. Claim 48 was cancelled. Claims 39-47, 49-51 are under examination.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Withdrawn Objections And/Or Rejections

The objection to the disclosure as set forth at page 3 of the previous Office Action (12 November 2002, Paper No. 13) is *withdrawn* in view of the amendment (11 February 2003, Paper No. 16).

The rejection of claims 39-51 under 35 USC 112, first paragraph, scope of enablement as set forth at pages 3-6 of the previous Office Action (12 November 2002, Paper No. 13) is *withdrawn* in view of the amendment (11 February 2003, Paper No. 16).

The rejection of claims 39-51 under 35 USC 112, first paragraph, written description as set forth at pages 6-8 of the previous Office Action (12 November 2002, Paper No. 13) is *withdrawn* in view of the amendment (11 February 2003, Paper No. 16).

Priority

The Examiner stated in the last Office Action that Applicants were entitled to the priority of PCT Application No. PCT/US98/19330, filed 9/16/98.

Applicant contends that although the application demonstrated multiple biological activities for the PRO224 polypeptides, for priority purposes, Applicants rely on the result of the "in vitro antitumor assay" first disclosed in PCT/US99/28565 filed on 12/299, priority to which is claimed in this application. Applicant states that the effective filing date of the present application is December 2, 1999.

Applicant's arguments have been fully considered but not deemed persuasive for the following reasons. The "in vitro antitumor assay" was found not to be enabled for the claimed polypeptide (PRO224, SEQ ID NO:127). The Examiner has now determined the effective filing date to be July 13, 2001 (actual filing date of the instant application). Since the "in vitro antitumor assay" is not enabled, none of the priority dates for the "in vitro antitumor assay" are enabling.

Claim Rejections - 35 USC § 112, Second Paragraph

Claims 39-47, 49-51 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The basis for this rejection is set forth at page 8 of the previous Office Action (12 November 2002, Paper No. 13).

Applicant states that the foregoing amendments wherein such references "lacking its associated signal peptide" and "lacking its associated signal sequence", parts (b) and (d), have been deleted in the above claims. Applicant's arguments have been fully considered but not deemed persuasive because only part (d) of the instant claims has been amended to delete the instant references.

Claim Rejections - 35 USC § 112, First Paragraph, Enablement

Claims 39-47, 49-51 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The instant claims are drawn to an isolated polypeptide (SEQ ID NO:127) or the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 209263, wherein said polypeptide is capable of inhibiting neoplastic cell growth.

The specification teaches that the antiproliferative activity of various PRO polypeptides was determined in the investigational, disease-oriented in vitro anti-cancer drug discovery of the National Cancer Institute (NCI). The purpose of the screen is to initially evaluate the cytotoxic and/or cytostatic activity of the test compounds against different types of tumors. Sixty tumor cell lines were employed in the study (the NCI panel). The specification states that a test sample is considered positive if it shows at least 50% growth inhibitory effect at one or more concentration. The specification states that the results of the assays demonstrate that the positive testing PRO polypeptides are useful for inhibiting neoplastic growth in a number of different tumor cell types and may be used therapeutically therefore (page 218, lines 15-22 and page 222, lines 20-25).

The subject matter sought to be patented as defined by the claims is not supported by an enabling disclosure. The National Institutes of Health (NIH) cautions against over-interpreting the results of preliminary anti-cancer drug screens using their panel of cancer cell lines. According to their website, <http://dtp.nci.nih.gov/branches/btb/ivclsp.html>, the NIH states that their In Vitro Cell Line Screening Project "is designed to screen up to 20,000 compounds per year for *potential* anticancer activity. ... The aim is to prioritize *for further evaluation*, synthetic compounds or natural product samples showing selective growth inhibition or cell killing of particular tumor cell lines". NIH also offers a Primary Anti-Cancer Drug Screening Program in which "[a]dvancement of *potential* anticancer agents from identification in the in vitro screen to preclinical development is enhanced. ...to determine whether a given experimental agent or series of agents have *even minimal* anti-tumor activity" (see website http://dtp.nci.nih.gov/branches/btb/hfa.html). This evidence establishes that the NIH considers even an extensive in vitro screening to constitute a preliminary screen, and that further testing in vivo is required to determine whether or not any of the agents identified in the in vitro screen truly have anticancer activity.

The relevant literature does not state that the cell lines are model systems for cancer therapy. The literature does state that an *in vitro* screening of anti-cancer drugs against tumor explant tissue is a good model system for cancer therapy, since the results obtained in these screens correlate well with the results seen in therapy. See Lawrence *et al.* (1999, Anti-Cancer Drugs 10:655-661) who state that screening anti-cancer drugs on freshly explanted tumor cells kept alive in a soft agar culture system,

called the human tumor cloning system, is an excellent model system, since the results obtained in the system correlate well with the results obtained in therapy (see paragraph bridging pp. 655-656). Hanauske *et al.* (1995, Investigational New Drugs 13: 43-49) also state that this system provides results that correlate well with clinical data for cancers of unknown primary origin (p. 43, abstract). Similarly, Kornblith *et al.* (2003, Anticancer Research 23:543-548) state that ovarian cancer cells used in a similar system provide results in anti-cancer drug screenings that are highly correlative to clinical patterns of response (p. 546, first paragraph of Discussion section). Finally, Depenbrock *et al.* (1997, European Journal of Cancer 33:2404-2410) state that anticancer drug screenings using freshly isolated and cultured tumor cells give results which are more clinically relevant than screenings using established cancer cell lines (p. 2409, left column, first paragraph of Discussion). It is important to realize the key difference between the cells used in these studies and established cancer cell lines. Whereas it is true that all cancer cells (whether from tumors or established cell lines) are immortal, the cells from freshly isolated tumors are phenotypically the same as the tumor from which they were isolated, whereas cells in established cell lines have undergone numerous phenotypic changes. The cells used in the studies of the references discussed above were generated from freshly isolated tumors, and kept alive on a short-term basis in cell culture (*in vitro*) for the screening process. These cells are not established cell lines, which are kept alive in cell culture for a significant length of time, wherein cells with altered phenotypes emerge.

Applicant is encouraged to submit evidence (Declaration 37 CFR 1.132 or a publication) demonstrating the ability of the claimed polypeptide (PRO224, SEQ ID NO:127) to inhibit neoplastic cell growth in a primary neoplasm explant.

Due to the large quantity of experimentation necessary to demonstrate the efficacy of the claimed polypeptide for inhibiting neoplastic cell growth in a good model system for cancer therapy, the lack of direction/guidance presented in the specification regarding same, the complex nature of the invention, the contradictory state of the prior art regarding established cancer cell lines (see references) and the unpredictability of the results in established cancer cell lines (see discussion above and recited references), undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections - 35 USC § 102

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 39-47 are rejected under 35 U.S.C. 102(b) as being anticipated by Kato *et al.*, WO 99/43802. Kato *et al.* teach a polypeptide sequence that is 100% identical to SEQ ID NO:127 claimed in the instant application. Please see sequence query Appendix A and reference. Since a compound and all of its properties are inseparable (*In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963)), it would be inherent that if Kato *et al.* teach a polypeptide sequence that is 100% identical to SEQ ID NO:127, it would have the activity of inhibiting neoplastic growth.

Claim Rejections - 35 USC § 103

Claims 50 and 51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kato *et al.*, WO 99/43802 in view of Boyle *et al.*, US Patent No. 6,284,485 B1. The teachings of Kato *et al.* are described above. Kato *et al.* do not teach chimeric polypeptides comprising epitope tags or an Fc region of an immunoglobulin.

Boyle *et al.* teach chimeric proteins wherein the polypeptides are fused to a heterologous sequence. The heterologous sequences include immunoglobulin fusions, such as Fc fusions (column 8, lines 27-34). It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of Kato *et al.* and Boyle *et al.* to make the instant invention of a chimeric polypeptide comprising SEQ ID NO:127 and an epitope tag or an Fc region of an immunoglobulin. The motivation and expected success is provided by Boyle *et al.* who teaches that heterologous sequences help aid in the activity and purification of the protein.

Claim Objection

Claim 49 is objected to for depending from a rejected claim.

Allowable Subject Matter

If the instant claims recite the following activity, "wherein the said polypeptide (PRO224, SEQ ID NO:127) induces redifferentiation of chondrocytes" (specification, page 235, Example 95, assay 110), the specification would be fully enabled as of the priority date determined by the Examiner (9/16/98) causing the withdrawal of the art rejection.

Conclusion

Claims 39-47, 50, 51 are rejected.

Claim 49 is objected to.

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Regina M. DeBerry whose telephone number is (703) 305-6915. The examiner can normally be reached on 9:00 a.m.-6:00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (703) 308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

RMD
August 23, 2003

Appendix A

GenCore version 4.5

OM protein - protein search, using sw model

Run on: September 13, 2002, 08:57:09 ; Search time 29.92 Seconds
(without alignments)
1046.885 Million cell updates/sec

Title: US-09-903-562B-127
Perfect score: 1503
Sequence: 1 MSGGWMAQVGAWRTGALGLA.....GLLVAMKESLLLSEQKTSLP 282

Scoring table: BLOSUM62
Gapop 10.0 , Gapext 0.5

Searched: 747574 seqs, 111073796 residues

Total number of hits satisfying chosen parameters: 747574

Minimum DB seq length: 0
Maximum DB seq length: 2000000000

Post-processing: Minimum Match 0%
Maximum Match 100%
Listing first 45 summaries

Database : A_Geneseq_032802:*
1: /SIDS1/gcgdata/hold-geneseq/geneseqp-embl/AA1980.DAT:*
2: /SIDS1/gcgdata/hold-geneseq/geneseqp-embl/AA1981.DAT:*
3: /SIDS1/gcgdata/hold-geneseq/geneseqp-embl/AA1982.DAT:*
4: /SIDS1/gcgdata/hold-geneseq/geneseqp-embl/AA1983.DAT:*
5: /SIDS1/gcgdata/hold-geneseq/geneseqp-embl/AA1984.DAT:*
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7: /SIDS1/gcgdata/hold-geneseq/geneseqp-embl/AA1986.DAT:*
8: /SIDS1/gcgdata/hold-geneseq/geneseqp-embl/AA1987.DAT:*
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21: /SIDS1/gcgdata/hold-geneseq/geneseqp-embl/AA2000.DAT:*
22: /SIDS1/gcgdata/hold-geneseq/geneseqp-embl/AA2001.DAT:*

Pred. No. is the number of results predicted by chance to have a score greater than or equal to the score of the result being printed, and is derived by analysis of the total score distribution.

SUMMARIES

Result No.	Score	% Query Match	Length	DB	ID	Description
1	1503	100.0	282	20	AAY32926	Transmembrane doma

ALIGNMENTS

RESULT 1
AAY32926
ID AAY32926 standard; Protein; 282 AA.
XX
AC AAY32926;
XX
DT 04-NOV-1999 (first entry)
XX
DE Transmembrane domain containing protein clone HP02375.
XX
KW Transmembrane domain containing protein; human; antibody production;
KW interaction assay; diagnosis; nutritional activity; cytokine;
KW cell proliferation; cell differentiation activity; immune stimulant;
KW immune suppressant; haematopoiesis regulator; tissue growth activity;
KW activin; inhibin activity; chemotaxis; chemokinesis; haemostasis;
KW thrombolysis; anti-inflammatory; cadherin; tumour invasion suppressor;
KW tumour inhibitor.
XX
OS Homo sapiens.
XX
PN WO9943802-A2.
XX
PD 02-SEP-1999.
XX
PF 25-FEB-1999; 99WO-JP00875.
XX
PR 27-FEB-1998; 98JP-0046607.
XX
PA (PROT-) PROTEGENE INC.
PA (SAGA) SAGAMI CHEM RES CENT.
XX
PI Kato S, Kimura T, Nakamura N, Sekine S;
XX
DR WPI; 1999-527617/44.

Appendix A

DR N-PSDB; AAZ11180, AAZ11187.
XX
PT New proteins and DNA useful for preventing tumours
XX
PS Claim 1; Page 73-74; 96pp; English.
XX
CC This sequence is a human transmembrane protein of the invention. The
CC DNAs are useful for expressing recombinant protein for analysis,
CC characterisation or therapeutic use, and are useful as markers for
CC tissues in which the corresponding protein is preferentially expressed.
CC They are also useful as molecular weight markers on Southern gels, as
CC chromosome markers or tags (when labelled) to identify potential genetic
CC disorders, as probes to hybridise and thus discover novel, related DNA
CC sequences, as a source of PCR primers for genetic fingerprinting, as
CC probes to subtract-out known sequences in the process of discovering
CC other novel DNAs, for selecting and making oligomers for attachment to a
CC gene chip or other support, including for examination of expression
CC patterns, to raise anti-protein antibodies using DNA immunisation
CC techniques, and as an antigen to raise anti-DNA antibodies or elicit
CC another immune response. Where the DNA encodes a protein which binds to
CC another protein (e.g. in a receptor-ligand interaction), the DNA can also
CC be used in interaction trap assays to identify DNAs encoding the other
CC protein with which binding occurs or to identify inhibitors of the
CC binding interaction. The DNAs and proteins can have e.g. nutritional
CC activity, cytokine and cell proliferation/differentiation activity,
CC immune stimulating (e.g. as vaccines) or suppressing activity,
CC haematopoiesis regulating activity, tissue growth activity,
CC activin/inhibin activity, chemotactic/chemokinetic activity, haemostatic
CC and thrombolytic activity, receptor/ligand activity, anti-inflammatory
CC activity, cadherin/tumour invasion suppressor activity, and tumour
CC inhibition activity.
XX
SQ Sequence 282 AA;

Query Match 100.0%; Score 1503; DB 20; Length 282;
Best Local Similarity 100.0%; Pred. No. 1.9e-112;
Matches 282; Conservative 0; Mismatches 0; Indels 0; Gaps 0;

```
Qy       1 MSGGWMAQVGAWRTGALGLALLLLLGLGLGLEAAASPLSTPTSAQAAGPSSGSCPPTKFQ 60
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1 msggwmaqvgawrtgalglalllllglglgleaaasplstptsaqaagpssgscpptkfq 60

Qy      61 CRTSGLCVPLTWRCDRDLDCSDGSDEEECRIEPCTQKGQCPPPPGLPCPCTGVSDCSGGT 120
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      61 crtsglcvpltwrcdrdldcsdgsdeeecriepctqkgqcppppglpcpctgvsdcsggt 120

Qy     121 DKKLRNCSRLACLAGELRCTLSDDCIPLTWRCDGHPDCPDSSDELGCGTNEILPEGDATT 180
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db     121 dkklrncsrlaclagelrctlsddcipltwrcdghpdcpdssdelgcgtneilpegdatt 180

Qy     181 MGPPVTLESVTSLRNATTMGPPVTLESVPSVGNATSSSAGDQSGSPTAYGVIAAAAVLSA 240
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db     181 mgppvtlesvtslrnattmgppvtlesvpsvgnatsssagdqsgsptaygviaaaavlsa 240

Qy     241 SLVTATLLLLSWLRAQERLRPLGLLVAMKESLLLSEQKTSLP 282
          ||||||||||||||||||||||||||||||||||||||||||||
Db     241 slvtatllllswlraqerlrplgllvamkeslllseqktslp 282
```